

FIG. 1

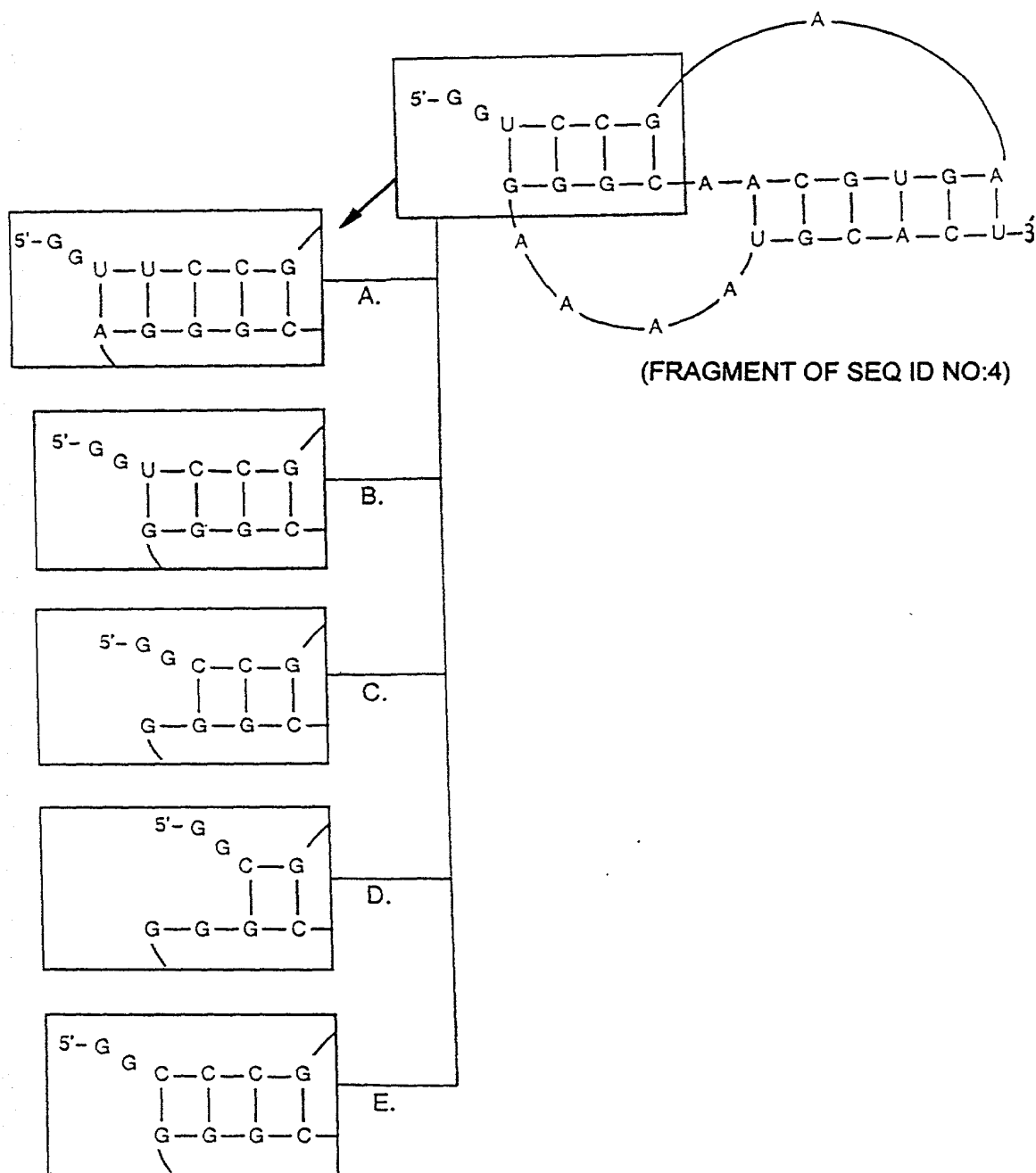


FIG. 2A

20200728404001

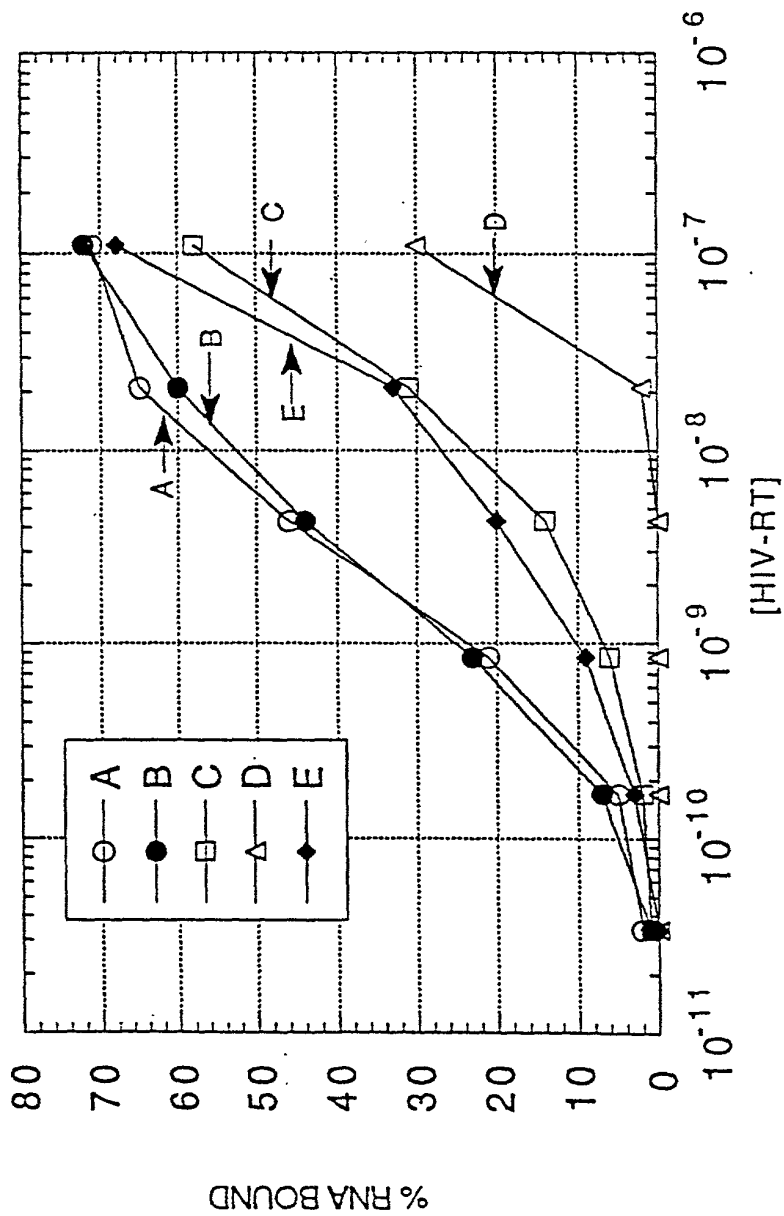


FIG.2B



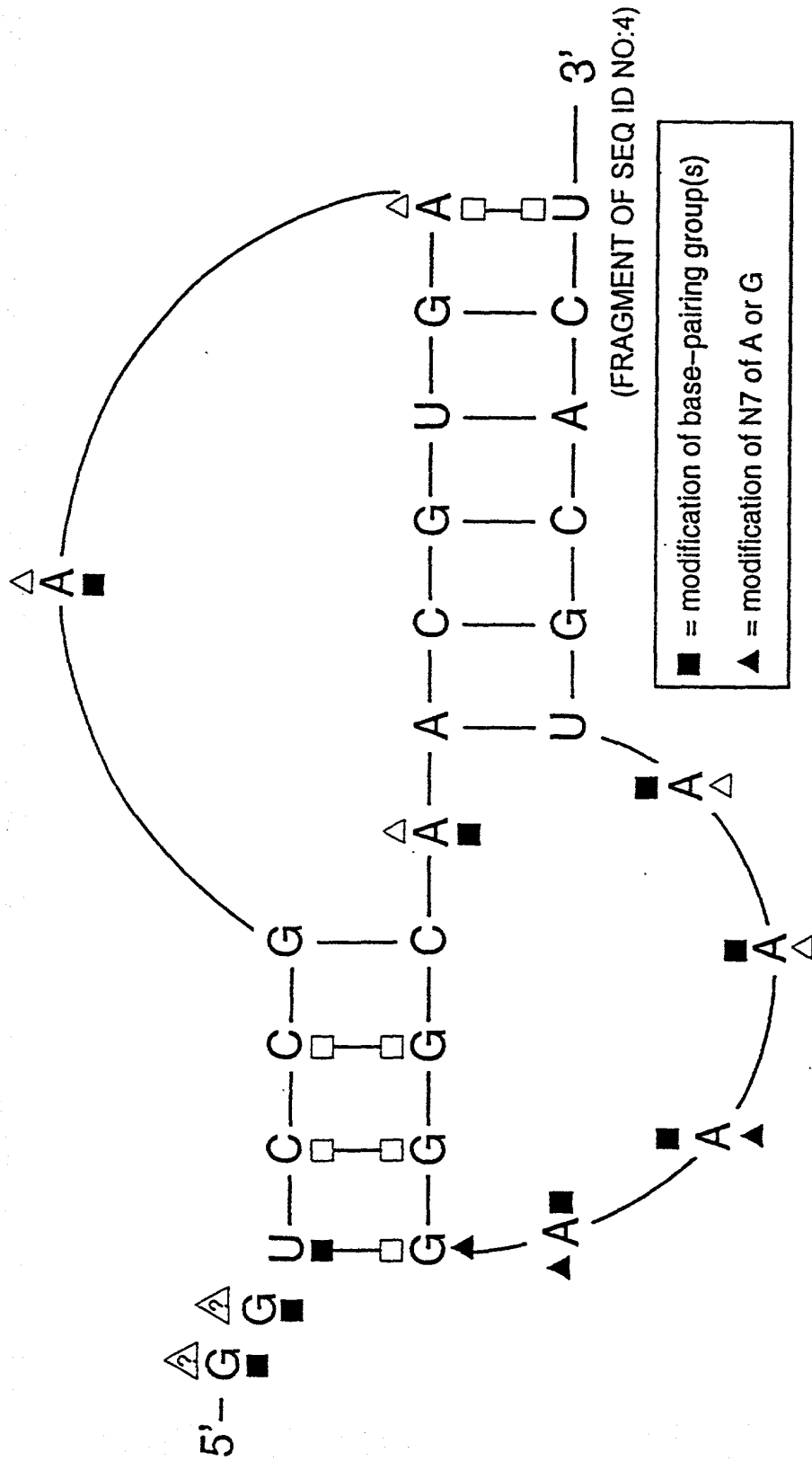


FIG. 4

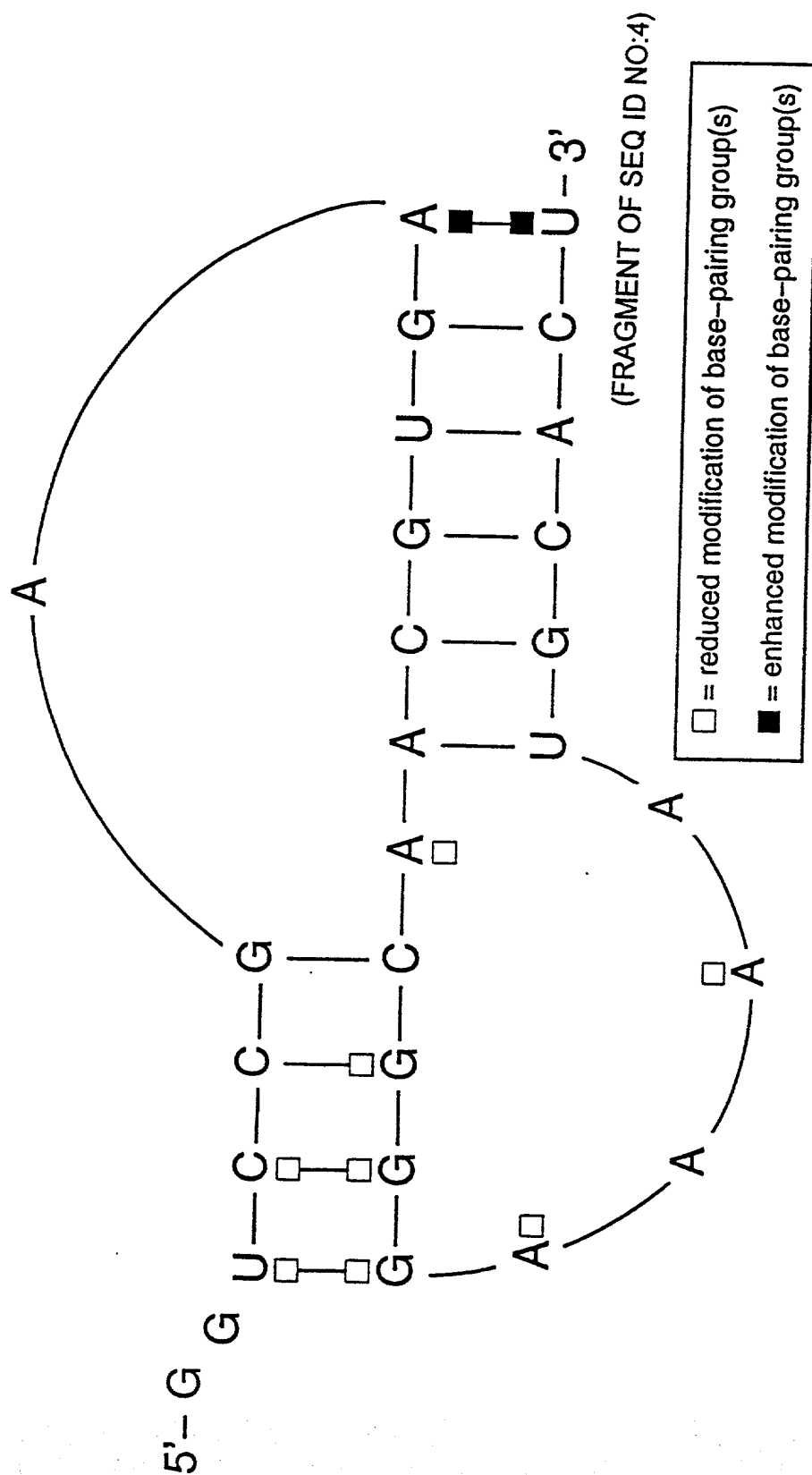


FIG. 5

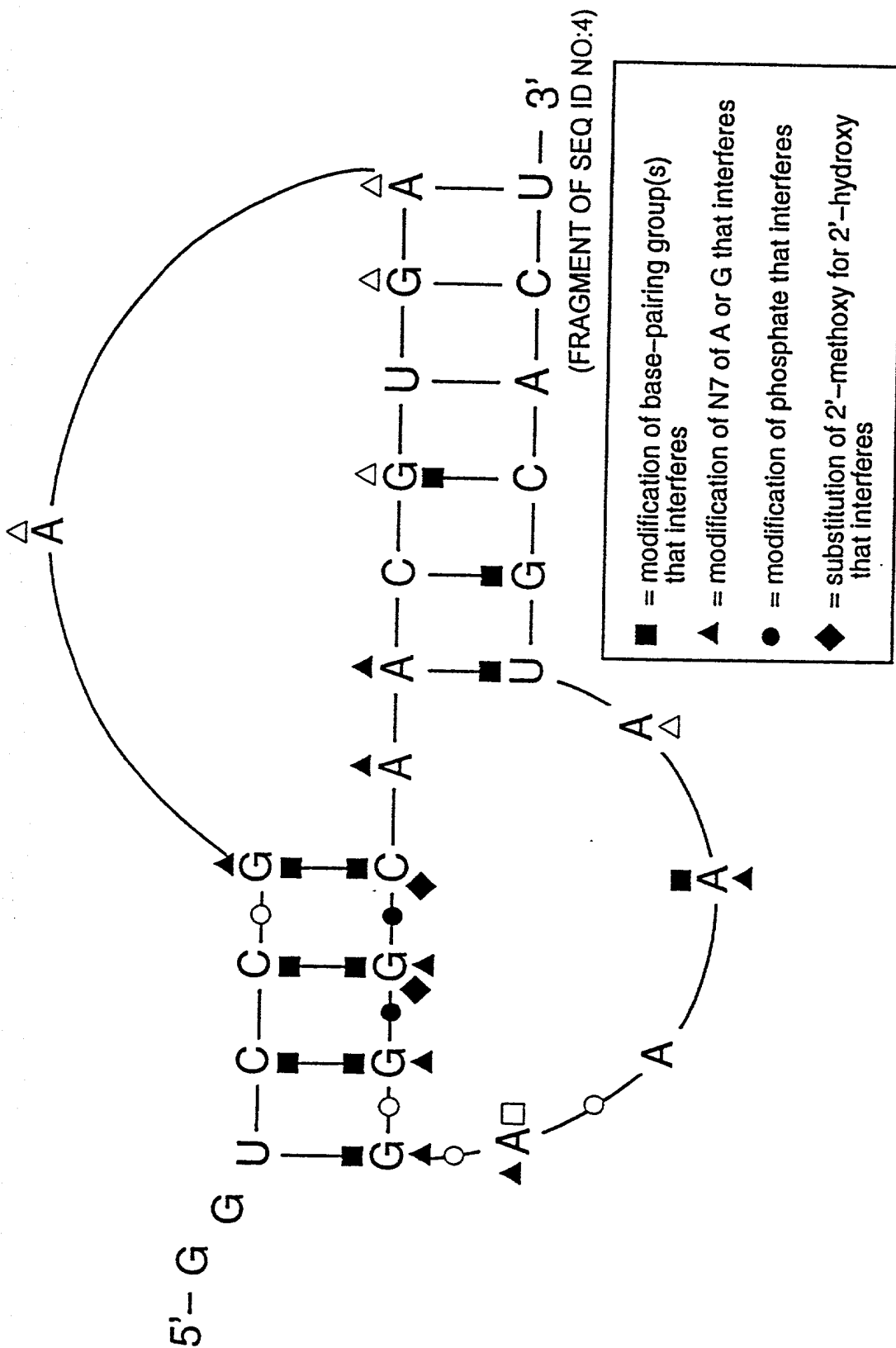
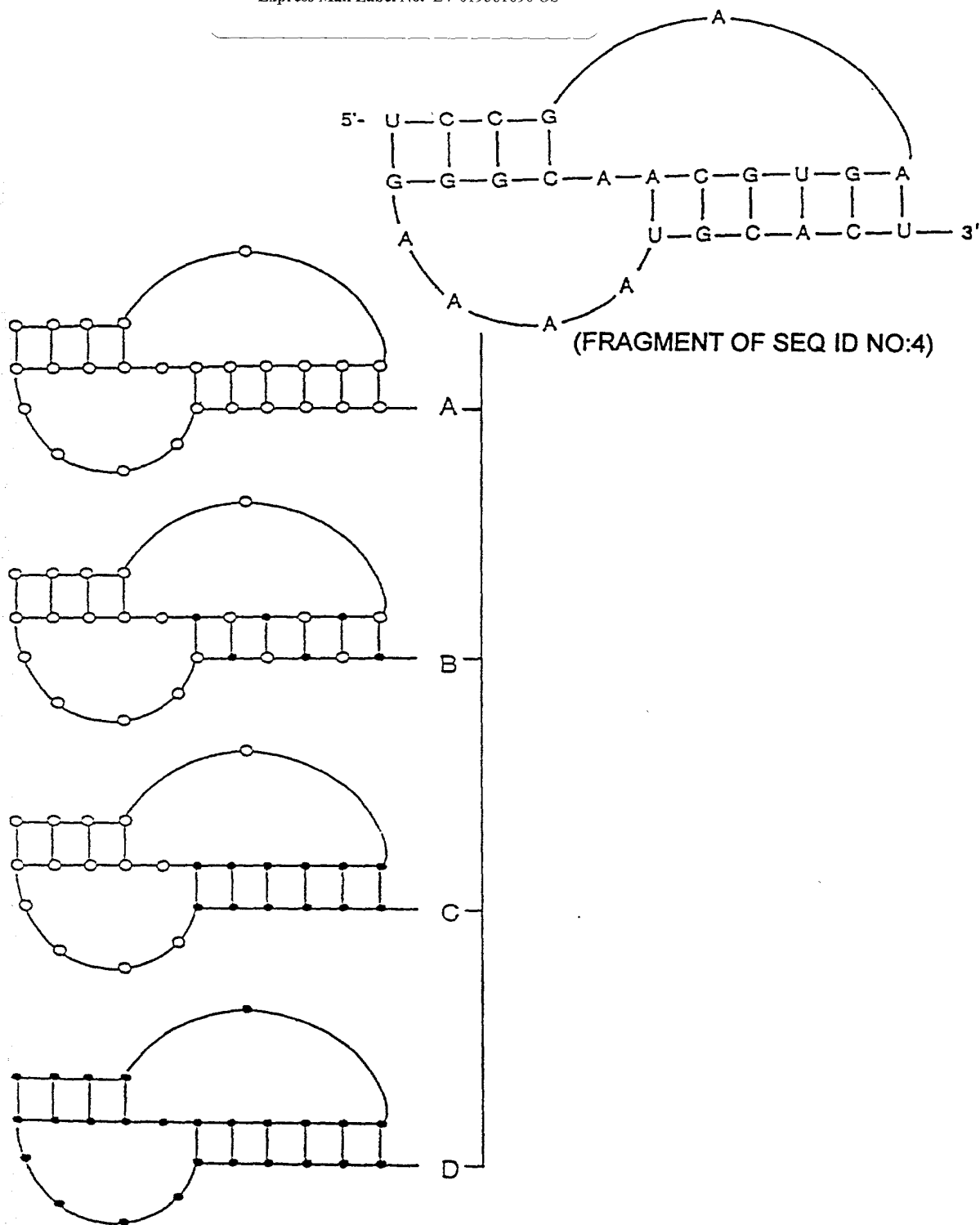


FIG. 6



● : denotes a 2' O-methyl instead of an OH,  
denoted by (O), at this position on the ribose

FIG. 7A



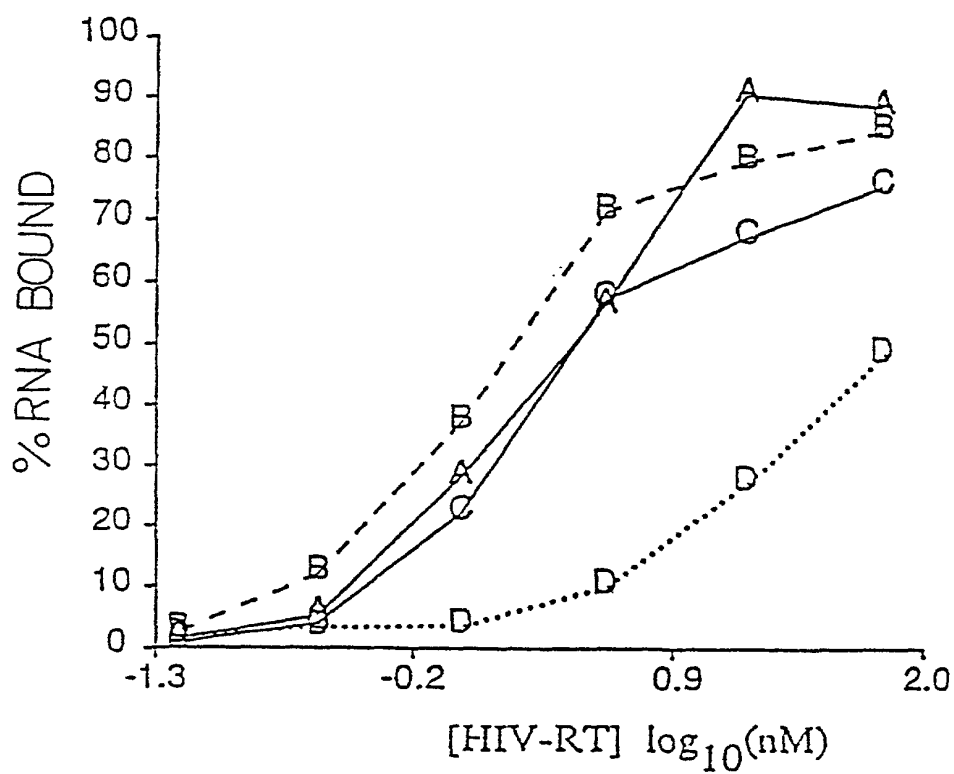


FIG.7B

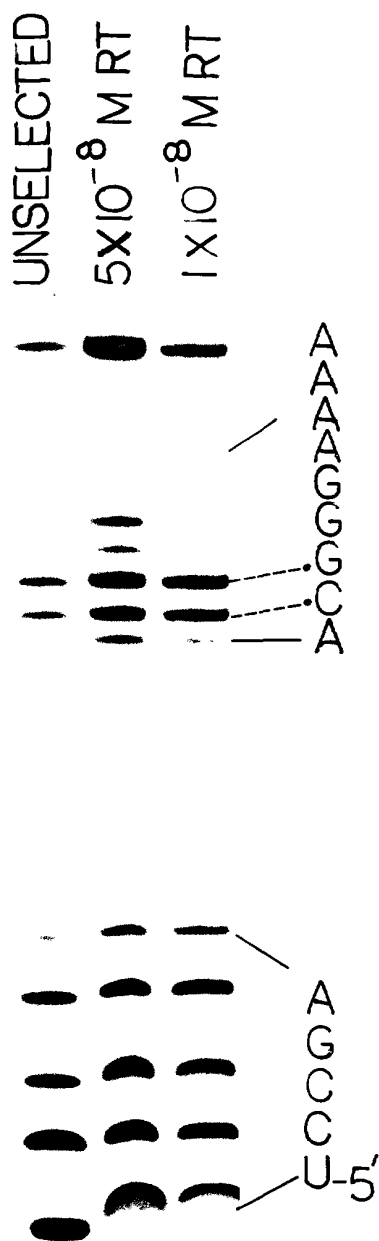


FIG. 8

5' -GGUCCGAAGUGCAACGGGAAAAUGCACU- [30N] -  
CUAUGAAAGAAUUUUUAUAUCUCUAUUGAAAC-3'

SEQ ID NO.: 37

Isolate number

SEQ ID NO:

3, 22, 29	uAGCUC <u>UGAGG</u> CUUU—CGU <u>GUGUUC</u> QAGcuau	14
14	uGCAU <u>UGAGG</u> CGGU—AA <u>GCGUUC</u> QUGcu	15
20	uGGUGA <u>UGAGG</u> CCG—AU <u>GCGUUC</u> QUGCCGcu	16
4	uGACG <u>UGAGG</u> UCUU—GGU <u>ACUGUUC</u> QUGGCUcu	17
30	uCU <u>GGUGAG</u> ACUUG—AA <u>GUGUUC</u> QCCAGGUcu	18
38	uCCCG <u>UGAAG</u> CAUA—AU <u>GCGUUC</u> QUGGGGUcu	19
39	uGGGA <u>UGAGG</u> UU—CC <u>CGUUC</u> QUGCCGCACCcu	20
2, 6, 9	uAGCGA <u>UGAAG</u> UGA—UA <u>CUGGUC</u> QAUCGUGcu	21
13, 26	uCA <u>CAUGAG</u> CCUU—CU <u>GUGGUC</u> QUGUGUGcu	22
7	uUGU <u>UGAGUG</u> GUUGAUU <u>CCAUGG</u> UCQAACcu	23
35	uGCCU <u>UGAGC</u> UGU—UU <u>AGCGGUC</u> QAGGUGCUcu	24
24	uCAAG <u>UGGAA</u> GACUU—AG <u>UCUGCUC</u> QUGUGcu	25
8	uUGCGU <u>CGAAG</u> UAA—UU <u>CUGGUC</u> GAUGCCAcu	26
40	uUUC <u>CAUGAG</u> GUAUG—UAAUGA <u>UGGUC</u> GUGCGCcu	27

1	uGCGG <u>GAGAG</u> UCUU—UU <u>GACGUUC</u> UCCUGCGcu	28
17	uCAUGG <u>GAGCC</u> AUCGA—UUC <u>UGGGUG</u> UUGCcuau	29
23, 27	uUGCAC <u>GAGCC</u> AAA—UU <u>UGGUGU</u> UGCUGUGcu	30
18, 34	uGGCC <u>GAGCU</u> UAAA—UUC <u>AAGUGU</u> UGCUGGCUcu	31
19	uCAUAGC <u>AGUC</u> UUGAUACUAUG <u>GAUGG</u> UGGcuau	32
37	uGGAUGC <u>AAGU</u> UAA—CU <u>CUGGUG</u> CAUCCGUCcu	33

31 uCAGUGGAGAUUAAGCCUCGCUAGGGGCGCcuau

34

FIG. 9

2020-01-07 10:40:49

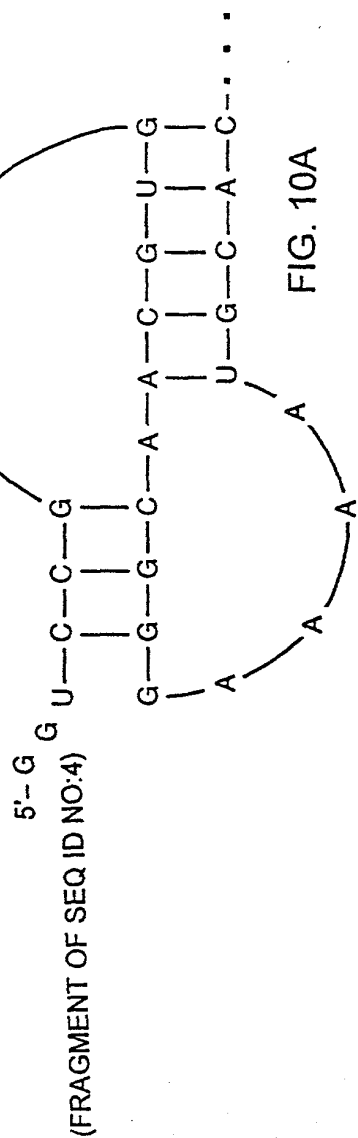
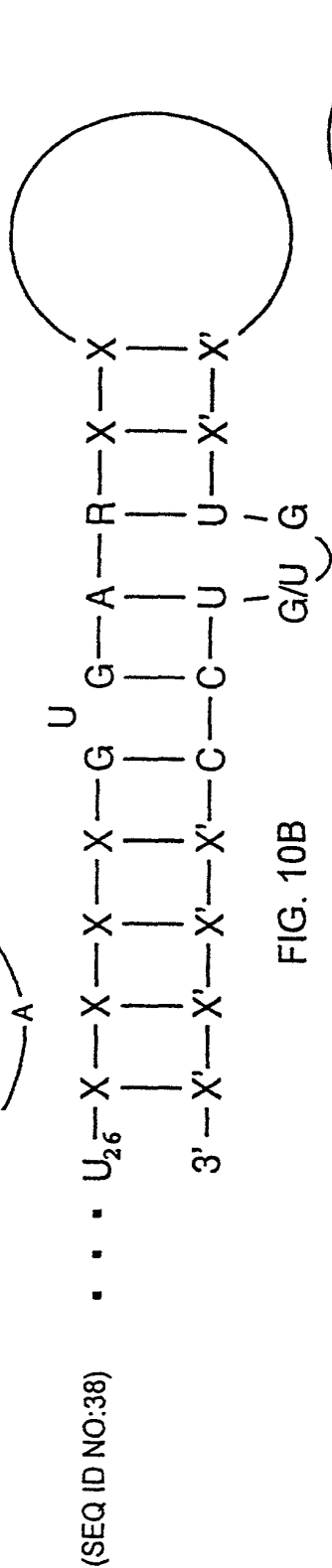


FIG. 10A



**FIG. 10B**

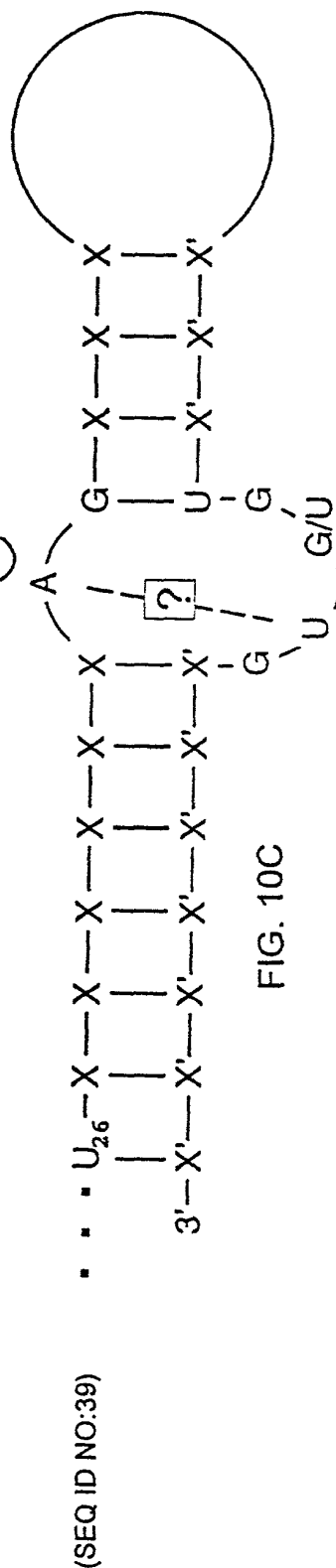


FIG. 10C

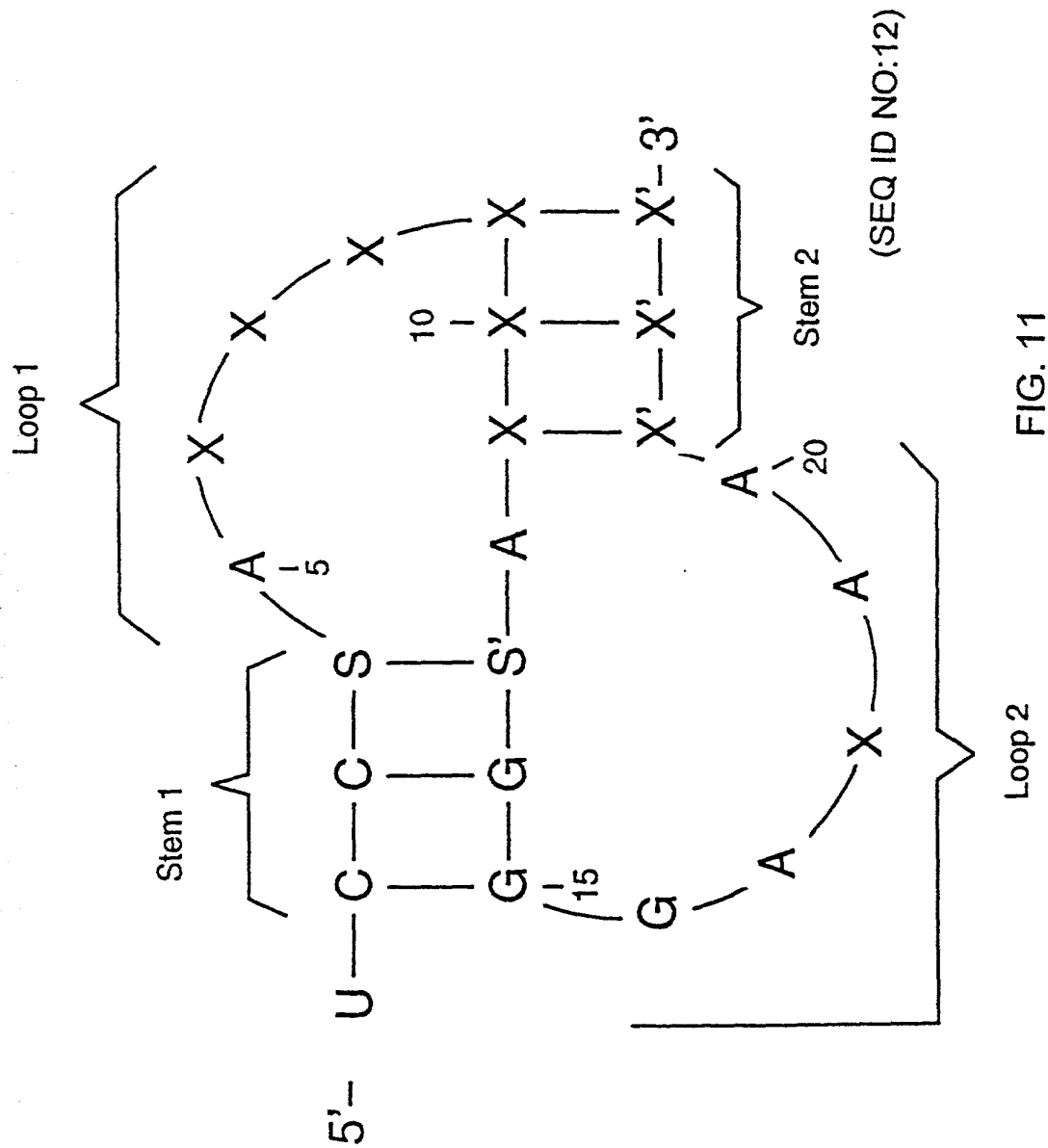


FIG. 11

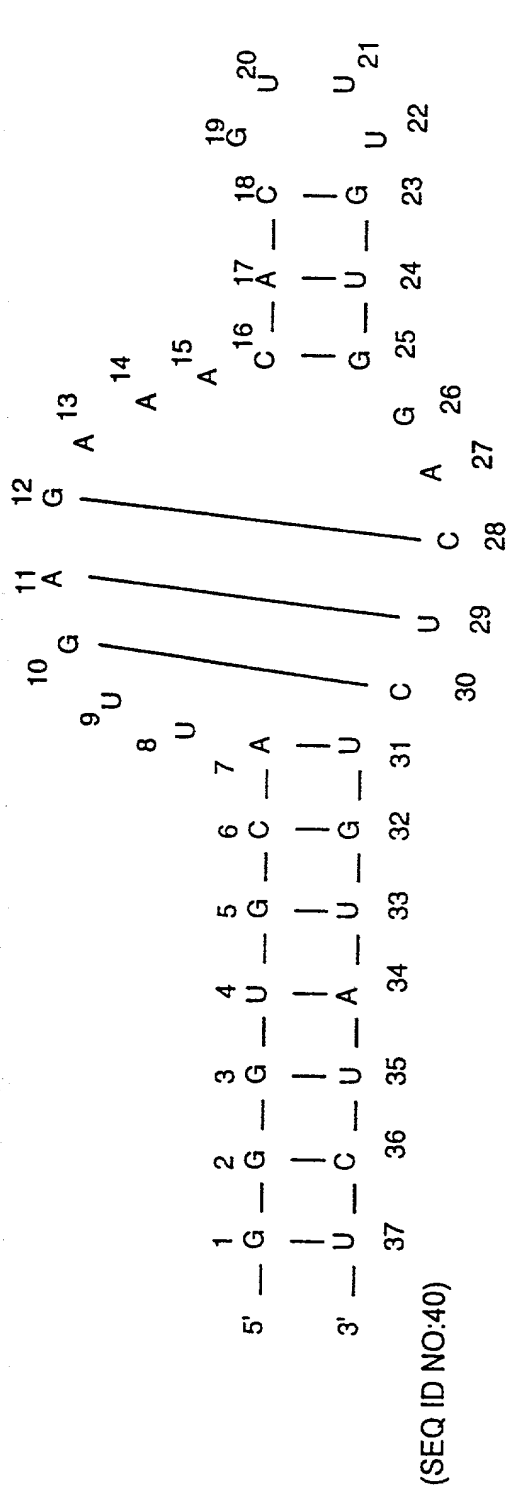


FIG. 12A

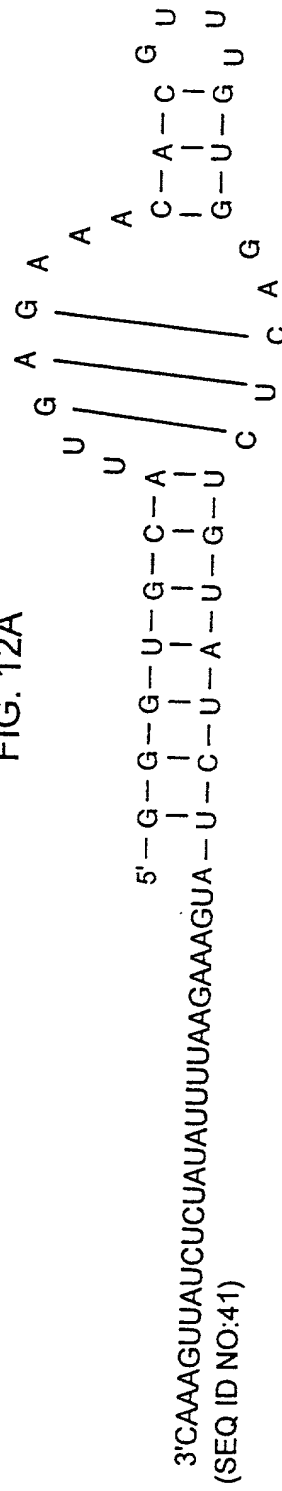


FIG. 12B

(SEQ ID NO:42) 5' GTTCAATAGAGATATAAAATTC 3'

FIG. 12C

modifying agent	partial		full
	less	more	
KETHOXAL	△	▲	▲
DMS	□	▨	■
CMCT	◇	◆	◆
DEPC	○	⊗	●

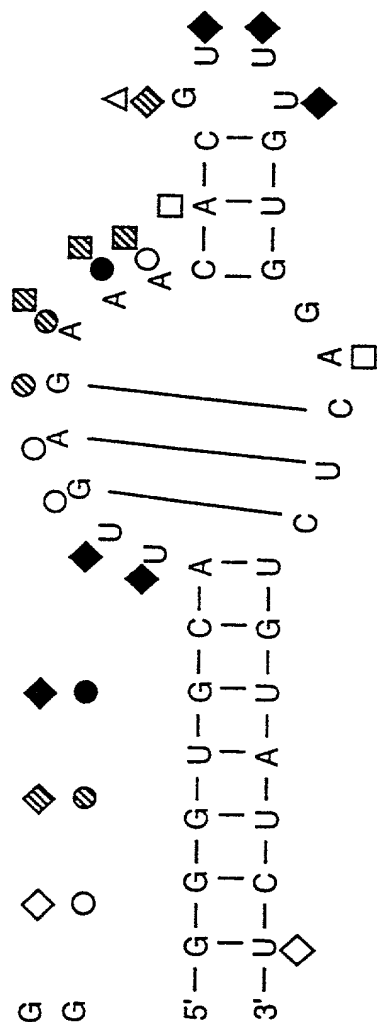
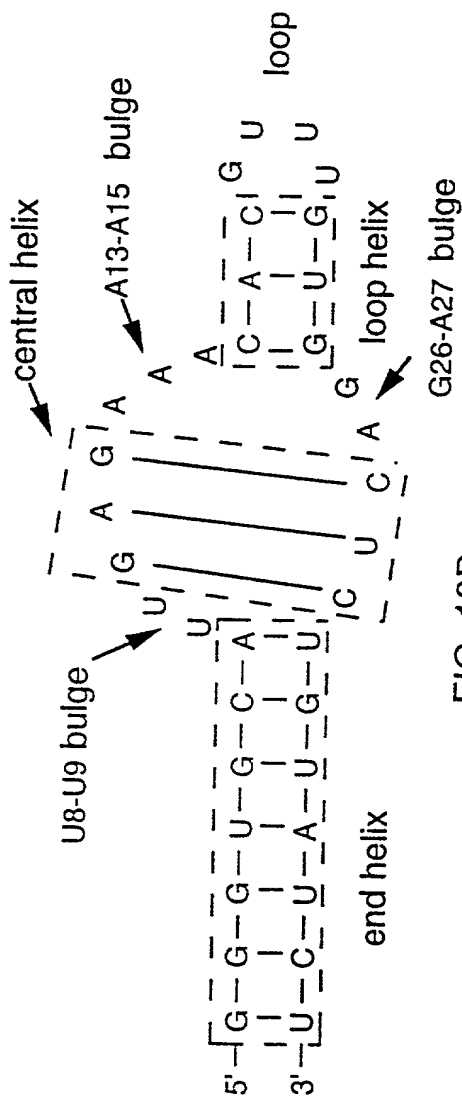
FIG. 13A  
(SEQ ID NO:40)

FIG. 13B

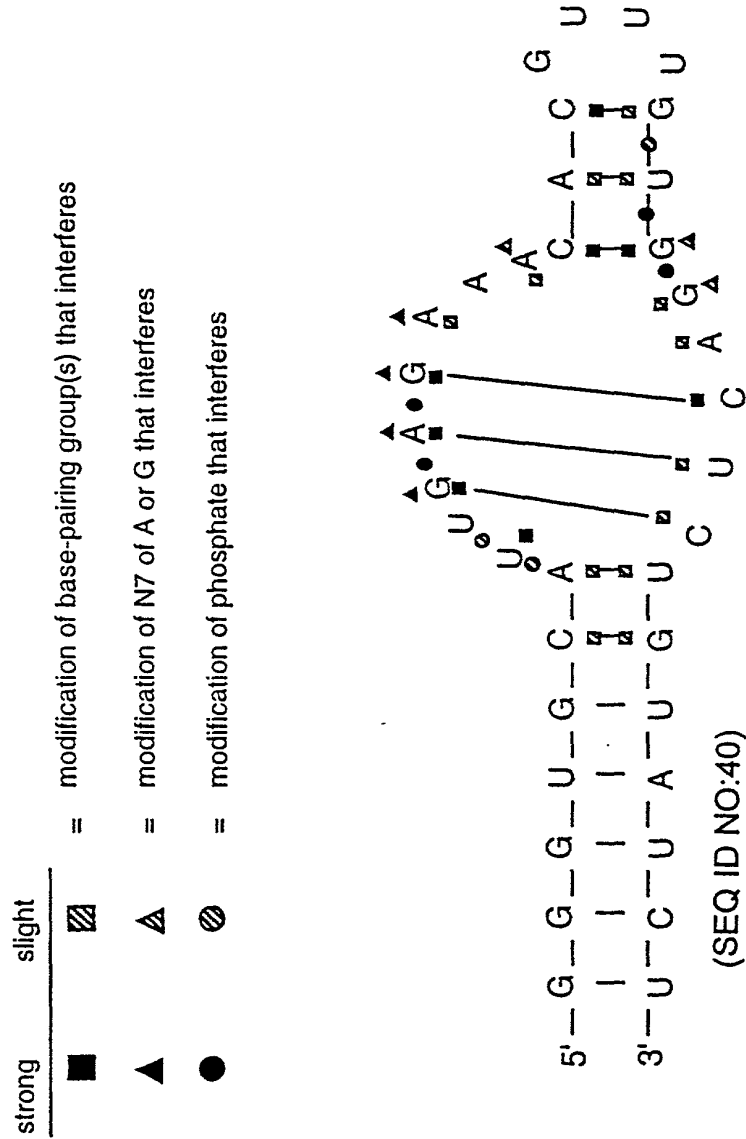


FIG. 14





FIG. 15



FIG. 16

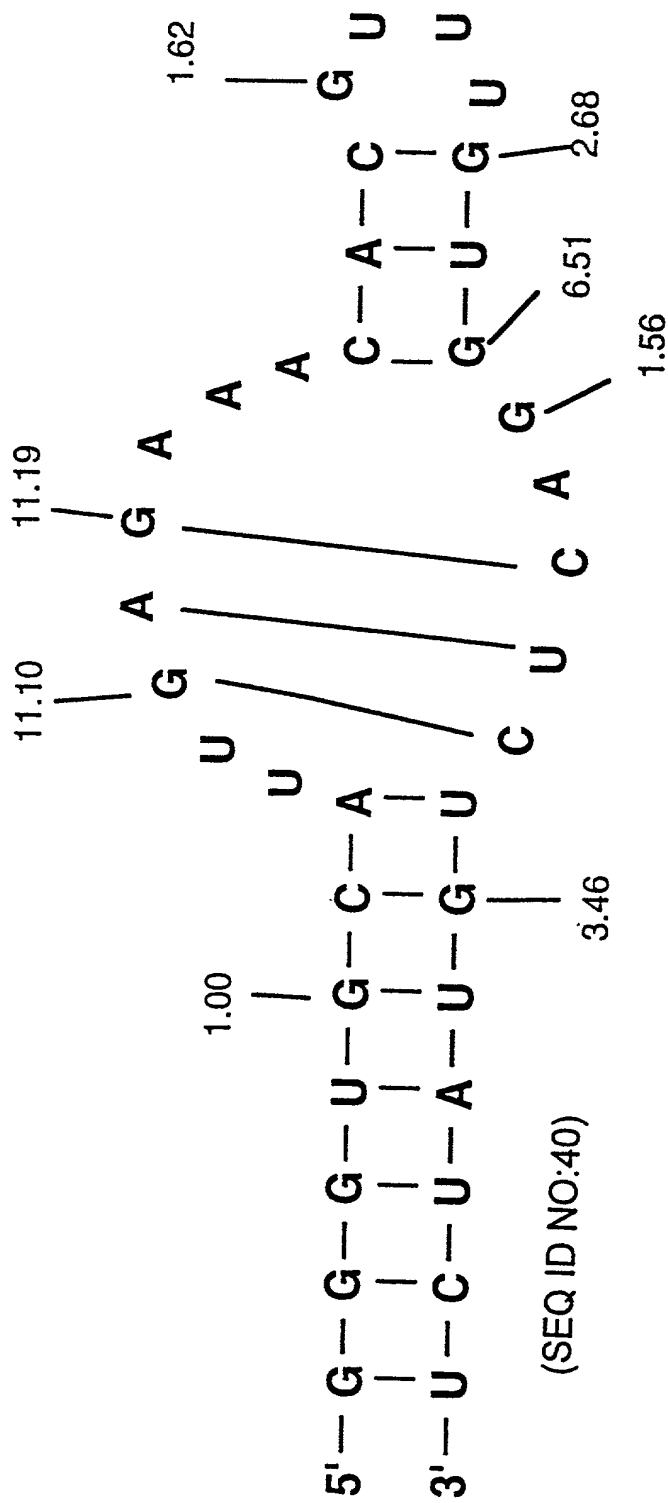
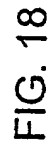


FIG. 17



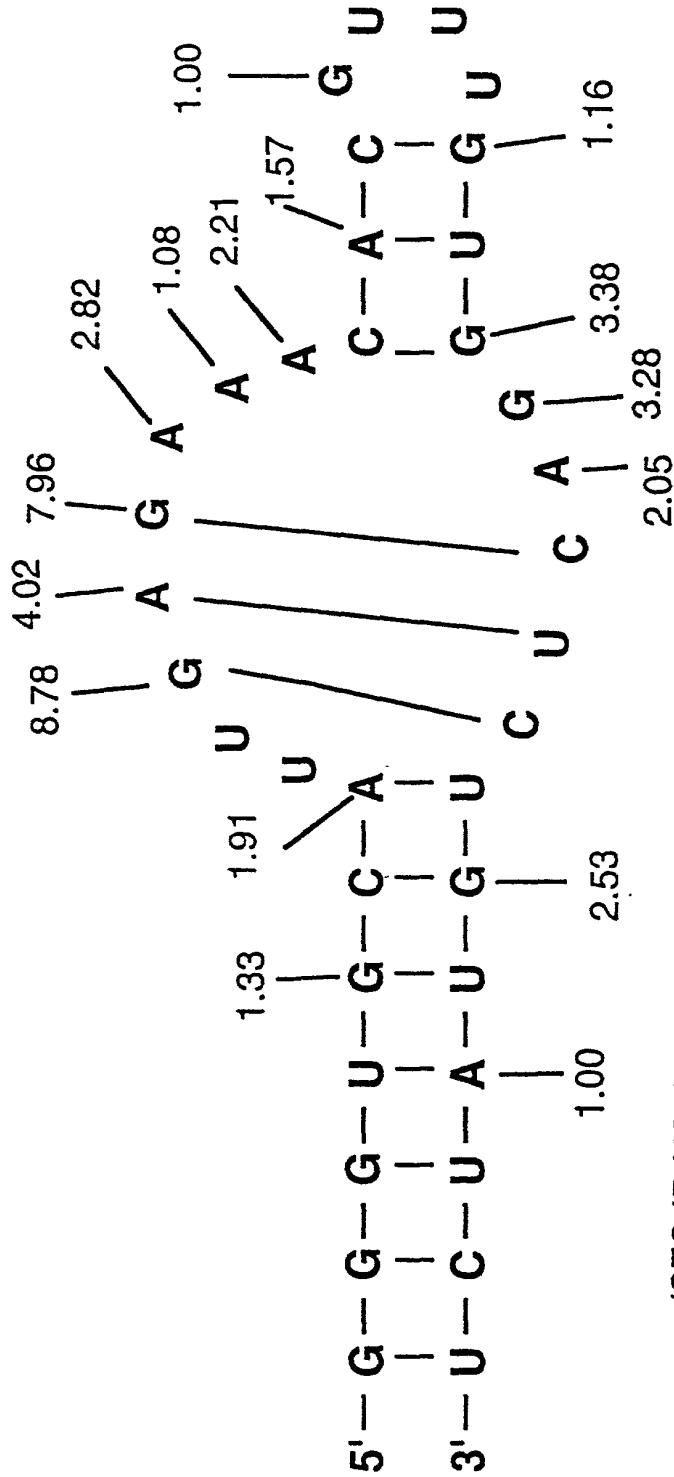


FIG. 19

5'-G-G-G-U-G-C-A  
| | | | |  
3'-U-C-U-A-U-G-U  
▲

U  
U  
G  
C  
U  
C  
U  
C  
A  
A  
A  
A  
G  
A  
G  
A  
G

(SEQ ID NO:40)

(SEQ ID NO:40)

SEQ ID NO.: 43

5' -GGGACUAUUGAUGGCCUCCGACC-6a-CACACAGAGUAAAGAGGAUCCGGG-3'

Biased ligand sequences

	SEQ ID NO.:
6a <u>GGGUGCAUUGAGAAACACGU-UUGGACUCUGUAUCU</u>	40
1 <u>UGGUGCGUUGAGAAACAGGU-UUUUGGACUCCGUACCA</u>	45
2 <u>GUAUGCAUUGAGAGUCACAC-UUGGACUCUGCAUCC</u>	46
3 <u>AGAUGGAUUGAGAAACACUA-UUAUGGACUCUCCAUCC</u>	47
4 <u>AGCUUCGUCGAGAUACACGU-UGAUGGACUCCGAAGCA</u>	48
5 <u>UCGUACGUUGAGAAACAAAGU-UUAUGGACUCUGUAACU</u>	49
6 <u>UCGAUCGUUGAGAUACACGC-UAGUGGACUCCGAAACU</u>	50
8 <u>UACUGCAUCGAGAUACACGU-UUGGACUCUGGACAU</u>	51
9 <u>UGAUACGUUGAGAAACACAA-UGCUGGACUCCGCAUCC</u>	52
10 <u>GCCUGCAUUGAGAAACAGGA-UUCUGGACUCUGCCACU</u>	53
12 <u>CGCUAUGUUGAGAAACACUU-UGCUGGACUCCGUAGCU</u>	54
13 <u>UACUGCAUCGAGAAACACGU-AAGUG-ACUCUGCAUCC</u>	55
15 <u>CGGUACGUUGGAGAUACACGA-AGAUGGACUCCGUAUCG</u>	56

FIG. 21-A

SEQ ID NO.:

17	<u>AA</u> <u>CU</u> <u>CC</u> <u>AU</u> <u>CG</u> <u>AG</u> <u>AA</u> <u>CA</u> <u>CGA</u> - <u>UA</u> <u>GU</u> <u>GG</u> <u>AC</u> <u>UC</u> <u>UG</u> <u>GAG</u> <u>CU</u>	57
18	<u>GG</u> <u>AG</u> <u>AC</u> <u>GU</u> <u>CG</u> <u>AG</u> <u>AA</u> <u>CA</u> <u>CGU</u> - <u>UU</u> <u>GU</u> <u>GG</u> <u>AC</u> <u>UC</u> <u>CG</u> <u>UC</u> <u>UCU</u>	58
21	<u>AG</u> <u>CU</u> <u>AC</u> <u>AU</u> <u>CG</u> <u>AG</u> <u>AA</u> <u>CA</u> <u>AGA</u> - <u>UU</u> <u>UU</u> <u>GG</u> <u>AC</u> <u>UC</u> <u>UG</u> <u>UAG</u> <u>CG</u>	59
23	<u>AA</u> <u>GU</u> <u>GC</u> <u>AU</u> <u>UG</u> <u>AG</u> <u>AA</u> <u>CA</u> <u>AAU</u> - <u>GA</u> <u>UU</u> <u>GG</u> <u>AC</u> <u>UC</u> <u>UG</u> <u>CA</u> <u>cac</u>	60
24	<u>UG</u> <u>CU</u> <u>AC</u> <u>GU</u> <u>UG</u> <u>AG</u> <u>AA</u> <u>CA</u> <u>CGU</u> - <u>UG</u> <u>AU</u> <u>GC</u> <u>AC</u> <u>UC</u> <u>CG</u> <u>UA</u> <u>AGCU</u>	61
25	<u>AG</u> <u>CU</u> <u>AC</u> <u>GU</u> <u>UG</u> <u>AG</u> <u>AA</u> <u>CA</u> <u>CGU</u> <u>U</u> <u>AC</u> <u>GUG</u> <u>G</u> - <u>CU</u> <u>CC</u> <u>GU</u> <u>AG</u> <u>CC</u>	62
27	<u>GAG</u> <u>UGG</u> <u>CU</u> <u>CG</u> <u>AG</u> <u>AA</u> <u>CA</u> <u>AGGU</u> - <u>UG</u> <u>CU</u> <u>GG</u> <u>AC</u> <u>UC</u> <u>GGC</u> <u>ACA</u> <u>U</u>	63
28	<u>UC</u> <u>GU</u> <u>GC</u> <u>GU</u> <u>CG</u> <u>AG</u> <u>AA</u> <u>CA</u> <u>CGU</u> - <u>UG</u> <u>AU</u> <u>GG</u> <u>AC</u> <u>UC</u> <u>CGC</u> <u>ACA</u> <u>G</u>	64
29	<u>GG</u> <u>CA</u> <u>CC</u> <u>GU</u> <u>UG</u> <u>AG</u> <u>AA</u> <u>CA</u> <u>CAU</u> - <u>GC</u> <u>GU</u> <u>GG</u> <u>AC</u> <u>UC</u> <u>CG</u> <u>UG</u> <u>CC</u>	65
30	<u>UCC</u> <u>UG</u> <u>CA</u> <u>UU</u> <u>G</u> <u>AG</u> <u>AA</u> <u>CA</u> <u>GUG</u> - <u>AU</u> <u>CU</u> <u>GG</u> <u>AC</u> <u>UC</u> <u>UG</u> <u>CA</u> <u>ACU</u>	66
31	<u>c</u> <u>U</u> <u>G</u> <u>U</u> <u>G</u> <u>G</u> <u>A</u> <u>U</u> <u>G</u> <u>A</u> <u>G</u> <u>C</u> <u>A</u> <u>A</u> <u>C</u> <u>A</u> <u>C</u> <u>GU</u> - <u>G</u> <u>A</u> <u>G</u> <u>U</u> <u>G</u> <u>G</u> <u>A</u> <u>C</u> <u>U</u> <u>C</u> <u>C</u> <u>A</u> <u>CAU</u>	67
32	<u>CC</u> <u>GU</u> <u>GC</u> <u>GU</u> <u>UG</u> <u>AG</u> <u>AA</u> <u>CA</u> <u>CAC</u> - <u>CG</u> <u>AU</u> <u>GG</u> <u>AC</u> <u>UC</u> <u>CG</u> <u>CA</u> <u>UGU</u>	68
33	<u>AG</u> <u>CU</u> <u>GC</u> <u>AU</u> <u>CG</u> <u>AG</u> <u>AA</u> <u>CA</u> <u>CGA</u> - <u>UU</u> <u>GU</u> <u>GG</u> <u>AC</u> <u>UC</u> <u>UG</u> <u>CAG</u> <u>CC</u>	69
35	<u>AG</u> <u>AU</u> <u>UC</u> <u>GU</u> <u>UG</u> <u>AG</u> <u>AA</u> <u>CA</u> <u>CAU</u> - <u>GG</u> <u>GU</u> <u>GG</u> <u>AC</u> <u>UC</u> <u>UCC</u> <u>CG</u> <u>CUA</u>	70
36	<u>AG</u> <u>AU</u> <u>GG</u> <u>AU</u> <u>UG</u> <u>AG</u> <u>AA</u> <u>CA</u> <u>CGU</u> - <u>UC</u> <u>GU</u> <u>GG</u> <u>AC</u> <u>UC</u> <u>UCC</u> <u>AA</u> <u>CU</u>	71
37	<u>GAC</u> <u>UG</u> <u>CA</u> <u>UC</u> <u>CG</u> <u>AG</u> <u>AA</u> <u>CA</u> <u>CUG</u> - <u>AU</u> <u>GUG</u> <u>GG</u> <u>CC</u> <u>UC</u> <u>CG</u> <u>CA</u> <u>CGG</u>	72

FIG. 21-B



SEQ ID NO.:

38	<u>AGCUACGUUGAGAAACA</u> <u>GUA</u> - <u>UAAUGGACUC</u> <u>CGUAGCU</u>	73
40	<u>GAGUGCGUCGAGAAACA</u> <u>CAU</u> - <u>UUGUGGACUC</u> <u>CGGACAC</u>	74
42	<u>UCGUACGUUGAGAAACA</u> <u>CCG</u> - <u>UAGUGGACUC</u> <u>CGUAUGU</u>	75
43	<u>AGAUA</u> <u>CGUUGAGAGACA</u> <u>CCG</u> - <u>ACGUGGACUC</u> <u>CGUAUCU</u>	76
44	<u>AGGAU</u> <u>CACAGAGAAA</u> <u>CACCGUGGUGG</u> - <u>CUC</u> <u>CCUCUAU</u>	77
45	<u>GUGCGCAUCGAGAAA</u> <u>CACGU</u> - <u>UGAUGGACUC</u> <u>UGCAUGCAC</u>	78
47	<u>GAGAGGAUCGAGAAA</u> <u>CACGU</u> - <u>AUGUGGACUC</u> <u>UCCAUUCU</u>	79
48	<u>GGAUGGAUUGAGACA</u> <u>CACGU</u> - <u>AUGUGGACUC</u> <u>UCCAUCA</u>	80
49	<u>UCGGGCAUUGAGAU</u> <u>ACACGU</u> - <u>AGAUGGACUC</u> <u>UGUCUCA</u>	81
50	<u>UGGACCGUA</u> <u>GAGAAA</u> <u>CACGUUGAUGG</u> - <u>CUC</u> <u>CCUCUGU</u>	82

FIG. 21-C

6a	G	G	G	U	G	C	A	U	U	G	A	G	A	A	A	C	A	C
wt	10	19	16	30	20	31	18	37	22	38	38	38	36	25	38	38	38	30
A	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
A	12	8	8	5	11	0	18	0	2	0	38	0	36	25	38	0	38	3
C	3	8	14	1	3	31	1	1	14	0	0	0	2	2	0	38	0	30
G	10	19	16	2	20	4	19	0	0	38	0	38	0	2	0	0	0	5
U	19	2	0	30	4	1	0	37	22	0	0	0	0	9	0	0	0	0
bp	16	20	26	31	33	35	35			38	38	38				38	38	26

FIG. 22A-1

6a	G	G	G	U	G	C	A	U	U	G	A	G	A	A	A	C	A	C
wt	.26	.50	.42	.79	.53	.82	.47	.97	.58	1.00	1.00	1.00	.95	.66	1.00	1.00	1.00	.79
D	.00	.03	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00
A	.32	.21	.21	.13	.29	.00	.47	.00	.05	.00	1.00	.00	.95	.66	1.00	.00	1.00	.08
C	.08	.21	.37	.03	.08	.82	.03	.03	.37	.00	.00	.00	.05	.05	.00	1.00	.00	.79
G	.26	.50	.42	.05	.53	.11	.50	.00	.00	1.00	.00	1.00	.00	.05	.00	.00	.00	.13
U	.50	.05	.00	.79	.11	.03	.00	.97	.58	.00	.00	.00	.00	.24	.00	.00	.00	.00
bp	.42	.53	.68	.82	.87	.92	.92	.00	.00	1.00	1.00	1.00	.00	.00	.00	1.00	1.00	.68

FIG. 22B-1

G	U	space	U	U	G	U	G	G	A	C	U	C	U	G	U	A	U	C	U
25	22	35	23	14	19	38	38	37	36	38	38	38	15	28	17	31	15	26	19
0	0	35	0	0	0	0	0	1	3	0	0	0	0	0	0	0	0	0	0
7	8	0	9	7	11	0	0	0	36	0	0	0	2	0	0	31	4	7	3
1	5	0	1	4	5	0	0	0	0	38	0	38	20	9	1	6	10	26	11
25	3	0	5	13	19	0	38	37	0	0	0	0	1	28	1	1	9	5	5
5	22	3	23	14	3	38	0	0	0	0	38	0	17	0	15	0	15	0	19
18				18	26	38	38			38	38	38	35	35	33	31	26	20	16

FIG. 22A-2

G	U	space	U	U	G	U	G	G	A	C	U	C	U	G	U	A	U	C	U
.66	.58	.92	.61	.37	.50	1.00	1.00	.97	.95	1.00	1.00	1.00	.45	.74	.39	.82	.39	.68	.50
.00	.00	.92	.00	.00	.00	.00	.00	.03	.08	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00
.18	.21	.00	.24	.18	.29	.00	.00	.00	.95	.00	.00	.00	.00	.00	.05	.82	.11	.18	.08
.03	.13	.00	.03	.11	.13	.00	.00	.00	.00	1.00	.00	1.00	.53	.24	.53	.16	.26	.68	.29
.66	.08	.00	.13	.34	.50	.00	1.00	.97	.00	.00	.00	.00	.03	.74	.03	.03	.24	.13	.13
.13	.58	.08	.61	.37	.08	1.00	.00	.00	.00	.00	1.00	.00	.45	.00	.39	.00	.39	.00	.50
.47	.00	.00	.00	.47	.68	1.00	1.00	.00	.00	1.00	1.00	1.00	.92	.92	.87	.82	.68	.53	.42

FIG. 22B-2

6a	G	G	G	U	G	U	G	C	A	U	G	A	G	A	A	C	A	C
wt	-.37	-.13	-.21	.16	-.10	.19	-.16	.34	-.05	.37	.37	.37	.32	.03	.37	.37	.37	.16
A	.19	.09	.09	.01	.16	-.13	-.16	-.13	-.07	-.13	.37	.37	.32	.03	.37	-.13	.37	-.05
C	-.05	.09	.24	-.09	-.05	.19	-.10	-.10	.24	-.13	.37	.37	-.07	-.07	-.13	.37	-.13	.16
G	-.37	-.13	-.21	-.07	-.10	-.02	.38	-.13	-.13	.37	.37	.37	-.13	-.07	-.13	-.13	-.13	.01
U	.38	-.07	-.13	.16	-.02	-.10	-.13	.34	-.05	-.13	-.13	-.13	-.13	.11	-.13	-.13	-.13	-.13

FIG. 22C-1



202070-2640400F

G	U	space	U	U	G	U	G	G	A	C	U	C	U	G	U	A	U	C	U
.03	-.05		-.02	-.26	-.13	.37	.37	.34	.32	.37	.37	.37	.11	-.18	-.24	.19	-.24	.05	-.13
.06	.09		.11	.06	.16	-.13	-.13	-.13	.32	-.13	-.13	-.13	-.13	-.13	-.07	.19	-.02	.06	-.05
-.10	.01		-.10	-.02	.01	-.13	-.13	-.13	-.13	.37	-.13	.37	.11	.40	.03	.03	.14	.05	.16
.03	-.05		.01	.22	-.13	-.13	.37	.34	-.13	-.13	-.13	-.13	.11	-.10	-.10	-.10	.11	.01	.01
.01	-.05		-.02	.26	-.05	.37	-.13	-.13	-.13	-.13	.37	-.13	-.13	.11	-.24	-.13	-.24	-.13	-.13



FIG. 22C-2

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6a	G1/U37	G2/C36	G3/U35	U4/A34	G5/U33	C6/G32	A7/U31	C16/G25	A17/U24	C18/G23	G19/U22
WT	2	16	8	28	2	28	16	38	38	19	9
AU	6	0	6	0	10	0	16	0	38	0	2
UA	2	1	0	28	2	0	0	0	0	2	1
GC	5	16	7	2	18	6	18	0	0	3	3
CG	1	2	8	0	1	28	1	38	0	19	1
GJ	1	1	8	0	2	0	1	0	0	1	9
UG	4	1	0	0	0	1	0	0	0	0	0
AC	3	3	0	2	1	0	2	0	0	0	1
CA	1	1	2	0	0	0	0	0	0	9	0
other	16	13	7	8	2	3	0	0	0	4	14

FIG. 23A

6a	G1/U37	G2/C36	G3/U35	U4/A34	G5/U33	C6/G32	A7/U31	C16/G25	A17/U24	C18/G23	G19/U22
WT	.05	.42	.21	.74	.05	.74	.42	1.00	1.00	.50	.24
AU	.16	.00	.16	.00	.26	.00	.42	.00	1.00	.00	.05
UA	.05	.03	.00	.74	.05	.00	.00	.00	.00	.05	.03
GC	.13	.42	.18	.05	.47	.16	.47	.00	.00	.08	.08
CG	.03	.05	.21	.00	.03	.74	.03	1.00	.00	.50	.03
GJ	.03	.03	.21	.00	.05	.00	.03	.00	.00	.03	.24
UG	.11	.03	.00	.00	.00	.03	.00	.00	.00	.00	.00
AC	.08	.08	.00	.05	.03	.00	.05	.00	.00	.00	.03
CA	.03	.03	.05	.00	.00	.00	.00	.00	.00	.24	.00
other	.42	.34	.18	.21	.05	.08	.00	.00	.00	.11	.37

FIG. 23B

6a	G1/U37	G2/C36	G3/U35	U4/A34	G5/U33	C6/G32	A7/U31	C16/G25	A17/U24	C18/G23	G19/U22
WT	-.34	.03	-.18	.35	-.34	.35	.03	.61	.61	.11	-.15
AU	.08	-.02	.08	-.02	.19	-.02	.03	-.02	.61	-.02	-.03
UA	.04	.01	-.02	.35	.04	-.02	-.02	-.02	-.02	.04	.01
GC	.05	.03	.11	.04	.40	.14	.46	-.02	-.02	.06	.00
CG	.01	.04	.19	-.02	.01	.35	.01	.61	-.02	.11	.01
GU	-.34	-.05	-.18	-.02	-.34	-.02	-.05	-.02	-.08	.01	-.15
UG	.09	.01	-.02	-.08	-.02	-.05	-.02	-.08	-.02	-.08	-.02
AC	.06	.00	-.02	.04	.01	-.02	-.03	-.02	-.08	-.02	.01
CA	.01	.01	.04	-.08	-.02	-.08	-.02	-.08	-.02	.16	-.02
other	.17	.09	-.07	-.04	-.20	-.17	-.25	-.25	-.25	-.15	.12

FIG. 23C

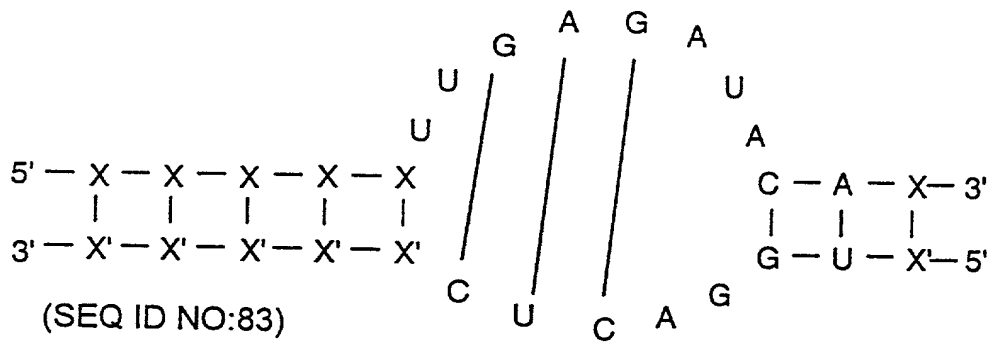


FIG. 24A

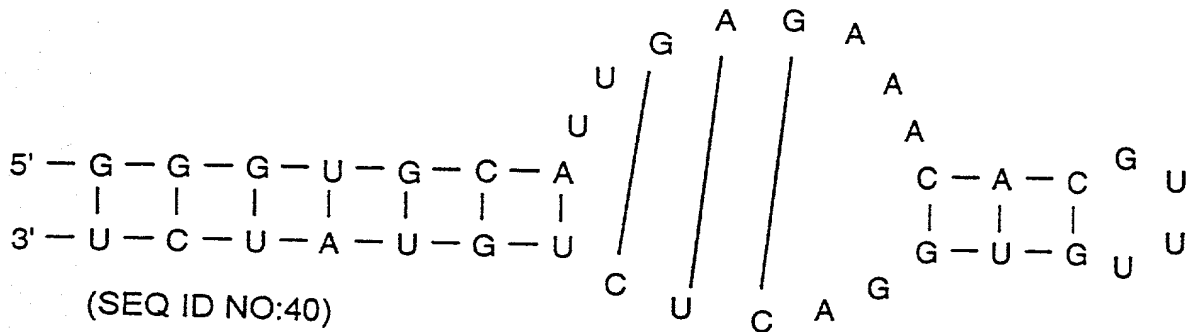


FIG. 24B

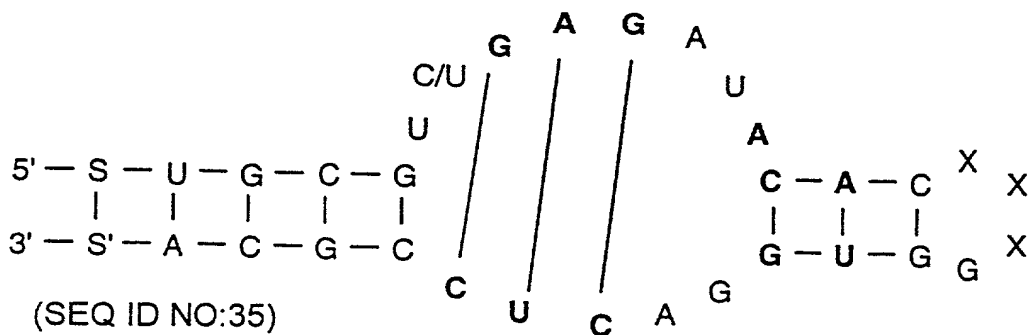


FIG. 24C

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